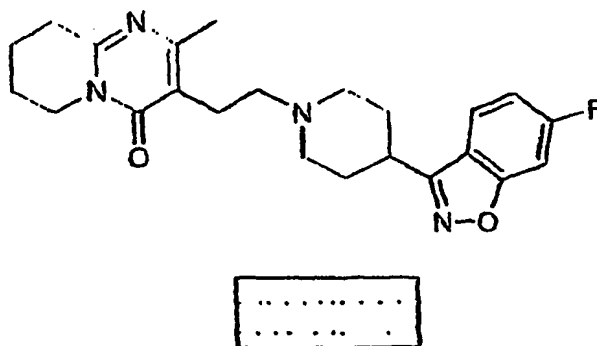


## PROCESS FOR THE PREPARATION OF RISPERIDONE

### Background of the Invention

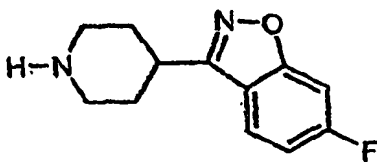
- 5 Risperidone is a new serotonin/dopamine antagonist belonging to a new class, the benzisoxazole. The structure of risperidone is shown in Formula -1. It is used for the treatment of schizophrenia and psychotic disorder.



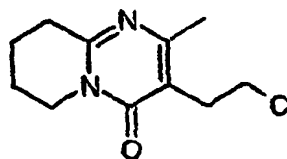
### Description of the Prior Art

- 10 Risperidone was first disclosed in US-A-4,804,663, according to which it may be prepared by the condensation of the benzisoxazole compound of Formula - 2 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole in its free base form and the tetrahydropyrimidine compound 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one of Formula - 3 in its hydrochloride salt form, in the
- 15 presence of sodium carbonate as a base (condensing agent) and potassium iodide as a catalyst in dimethylformamide (DMF) medium (Scheme-1), followed by standard work-up to get crude Risperidone, which is recrystallized in a mixture of dimethylformamide and isopropyl alcohol to get pure Risperidone with an overall yield of 46%.

20



**Benzisoxazole  
Formula- 2**



**Tetrahydropyrimidine  
Formula - 3**

WO-A-02/14256 and WO-A-02/12200 disclose another process for producing risperidone, in which the condensation of the intermediates of Formula - 2 and Formula - 3, in their free base forms, is carried out in isopropyl alcohol or methylethylketone solvent medium, using sodium carbonate as a base (condensing agent). The overall yield as described here is 60%.

Recently, WO-A-01/185731 describes a process for producing risperidone starting from the same two intermediates of Formula - 2 and Formula - 3, as free base, in the presence of sodium carbonate (condensing agent), but in water medium. Risperidone precipitates as a solid and is filtered and crystallised from dimethylformamide. The overall yield as described here is 65%.

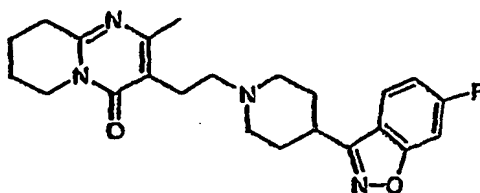
The benzisoxazole of Formula - 2, 6-fluoro-3- (4-piperidiny1)-1,2-benzisoxazole and tetrahydropyrimidine of Formula - 3, 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one are basic nitrogen heterocyclic derivatives that are solids with low melting points. These two intermediates, in particular the tetrahydropyrimidine of Formula - 3, are not stable, on account of their susceptibility to aerial oxidation. Therefore, these intermediates are usually isolated as acid addition salts, and are purified and stored as their acid addition salts, for example their hydrochloride salts. According to the above prior art processes, these acid addition salts have to be converted to the free base forms from the hydrochloride salts, before being subjected to condensation. These steps involve additional operations, which consume time and energy. Also, it is observed that impurities are formed while performing the set-free of said hydrochloride.

The present invention addresses these drawbacks and provides a simple and efficient process for producing risperidone from the stable hydrochloride salts of the two intermediates of Formula - 2 and Formula - 3. Advantageously, the

present invention allows risperidone to be produced by an easily operated process with minimal operation steps and a reduced effluent load.

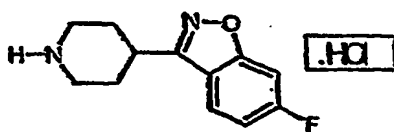
### Summary of the Invention

- 5 Accordingly, the present invention provides a process for the preparation of risperidone of Formula - 1:

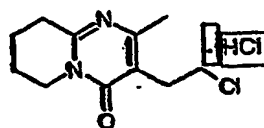


Formula -1

- 10 which process comprises reacting, in a condensation reaction, 6-fluoro-3-(4-piperidyl)-1,2-benzisoxazole monohydrochloride of Formula -2 with 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,a]pyrimidin-4-one monohydrochloride of Formula -3 :



Formula-2. HCl



Formula -3. HCl

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In a first embodiment, the condensation reaction is carried out in the presence of a base (condensing agent), in a solvent medium of water, one or more water-miscible solvents or a mixture of water and one or more water-miscible solvents, and the process comprises:

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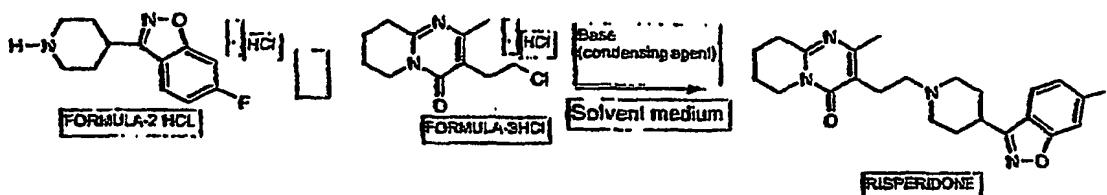
- a) carrying out the condensation reaction at a temperature in the range from 25 to 90°C;

- (b) after completion of the condensation reaction, diluting the condensation reaction mass with ice-cold water to precipitate risperidone;
- (c) filtering and drying the precipitated risperidone to obtain crude risperidone;
- 5 and
- (d) crystallizing the crude risperidone in an aqueous solvent to produce pure risperidone.
- 10 In a second embodiment, the condensation reaction is carried out in the presence of a base (condensing agent), in a solvent medium of water, one or more water-miscible solvents or a mixture of water and one or more water-miscible solvents, and the process comprises:
- 15 a) carrying out the condensation reaction at a temperature in the range from 25 to 90°C;
- (b) after completion of the condensation reaction, then reaction mass is cooled to room temperature and diluting the condensation reaction mass
- 20 with water to precipitate risperidone;
- (c) extracting the precipitated risperidone of step (b) with a water-immiscible solvent;
- 25 (d) optionally subjecting the water-immiscible solvent extract to acid-base work-up followed by extraction with a water-immiscible solvent;
- (e) concentrating the extract resulting from step (c) or optional step (d) under reduced pressure to produce crude risperidone; and
- 30

(f) crystallizing the crude risperidone in an aqueous solvent to produce pure risperidone.

### Detailed Description of the Invention

- 5 According to the first part of the process of the invention, the intermediates of Formula - 2 and Formula - 3, as their hydrochloride salts, are used for the condensation reaction, to form risperidone according to the Scheme 1:



10

**Scheme 1:**

The condensation reaction is carried out in a solvent medium. The solvent medium may be water or one or more water-miscible organic solvents, or a mixture of water and one or more water-miscible organic solvents. Preferably, the solvent medium is water or a mixture of water and acetonitrile. Most preferably, the solvent medium is a mixture of water and acetonitrile.

The base (condensing agent) used according to the present invention may be an inorganic salt such as the carbonate, bicarbonate or hydroxide of an alkali metal or alkaline earth metal. Preferred as base is sodium carbonate or potassium carbonate, and most preferred as base is sodium carbonate.

The mole ratio of the base (condensing agent) with respect to the hydrochloride salt of the compound of Formula - 2 may be from 2.0:1 to 5.0:1, and more preferably is from 4.0:1 to 4.6:1. Most preferably, the ratio is 4.3:1.

25

The condensation reaction is carried out according to the present invention by dissolving or suspending both of the reactants and reagent in the solvent medium. The sequence of addition of the reactants and reagent is very important. The most preferred sequence is to dissolve or suspend the base (condensing agent) in a solvent medium as described above (preferably water or acetonitrile, more preferably acetonitrile), and then to add to this the hydrochloride salt of the compound of Formula - 2. The hydrochloride salt of the compound of Formula - 3 is dissolved in a solvent medium as described above (preferably water) and added to the reaction mixture.

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Preferably, the solution of the hydrochloride salt of the compound of Formula - 3 is added over a period of 1 to 5 hours, and the most preferably is added over a period of 4 to 5 hours. The slow addition of the solution of the hydrochloride of the compound of Formula - 3 to the reaction mixture is to avoid the decomposition of the intermediate of Formula - 3 under the reaction conditions, and thus enhances the yield and quality of the product risperidone.

15

The temperature of the reaction mixture during the addition of the solution of the hydrochloride salt of the compound of Formula - 3 is maintained in the range from 25 to 90°C. The temperature of the solution of the hydrochloride salt of the compound of Formula - 3 being added is also preferably maintained in this temperature range.

20

Thus, the condensation reaction is carried out at a temperature in the range from 25 to 90°C, preferably in the range from 40 to 90°C, and more preferably in the range from 50 to 75°C.

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After the completion of the addition of the solution of the hydrochloride salt of the compound of Formula - 3 the reaction mixture is maintained in the range from 25 to 90°C, preferably in the range from 40 to 90°C, and more preferably in the range from 50 to 75°C, for an additional 2 to 10 hours, and preferably for an

30

additional 4 to 8 hours. Most preferably the reaction mixture is stirred at the same temperature as that of the reaction mixture during the addition of the solution of the hydrochloride salt of the compound of Formula - 3, for the additional hours.

5

Finally the product is isolated by standard work-up, preferably by work-up (i) or (ii) as explained further below, and crystallised to produce pure risperidone as a crystalline solid:

10 (i) A typical work-up may comprise of diluting the reaction mixture with ice-cold water to precipitate risperidone, filtering and drying the precipitated residue to obtain crude risperidone.

(ii) Alternatively, the reaction mixture is cooled to room temperature and  
15 diluted with water to precipitate risperidone, and the precipitated risperidone is then extracted with a water-immiscible organic solvent such as methylene dichloride (i.e. dichloromethane), ethylene chloride, dichloroethane, ethyl acetate, toluene, benzene or chloroform, preferably methylene dichloride, to produce an organic extract. The organic extract is then worked up according to Method A or  
20 Method B explained below:

According to Method A, the organic extract (preferably methylene dichloride) is washed with water, treated with activated carbon, and finally concentrated under reduced pressure to obtain crude risperidone.

25

According to Method B, the organic extract (preferably methylene dichloride) is purified by typical acid-base work-up, preferably as follows: The organic extract (preferably methylene dichloride) is extracted with aqueous acid such as 10-25% aqueous acid, preferably 10-15% aqueous acid, for example formic acid, acetic  
30 acid, hydrochloric acid, hydrobromic acid or tartaric acid. Preferred is 10-15% aqueous hydrochloric acid. The aqueous acidic extract is optionally, but

preferably, washed with organic solvent such as toluene, methylene dichloride, dichloroethane or ethyl acetate, or mixtures thereof, preferably methylene dichloride. The aqueous acidic extract is cooled to 15-25°C and the pH adjusted to 8-9 at 15-25°C by addition of a base such as aqueous sodium or potassium hydroxide, aqueous sodium or potassium carbonate or bicarbonate, or liquor ammonia solution. Most preferred as base is liquor ammonia solution. The resulting reaction mixture is extracted with a water-immiscible organic solvent such as methylene dichloride, ethylene chloride or chloroform, preferably with methylene dichloride. The organic (preferably methylene dichloride) extract is washed with water, treated with activated carbon and finally concentrated under reduced pressure to obtain crude risperidone worked up according to Method B.

Then, the crude risperidone obtained from work-up (i) or from Method A or B in work-up (ii) is crystallised in an aqueous solvent, preferably 5-20% aqueous solvent, selected from aqueous acetone, aqueous methyl ethyl ketone, aqueous methyl isobutyl ketone, aqueous acetonitrile and aqueous dimethylformamide, preferably aqueous acetone, especially 10% aqueous acetone, to produce pure risperidone as a crystalline solid. By this method, it is possible to obtain directly a pharmaceutically acceptable grade of risperidone, for example having purity greater than 99% (as determined by HPLC).

The crystallisation is carried out in known manner, for example by dissolving the crude risperidone in the aqueous solvent at 50-70° to produce a clear solution, treating the solution with activated carbon, filtering, cooling to 0-5°C, and then separating the pure risperidone by filtration.

When crystallised from an aqueous ketonic solvent selected from aqueous acetone, aqueous methyl ethyl ketone and aqueous methyl isobutyl ketone, crystalline risperidone is obtained having a polymorphic form identical to that of risperidone obtained from the inventors' recrystallizing process as disclosed in US patent No US 4,804,663 i.e. crystallization from IPA / DMF mixture. This is

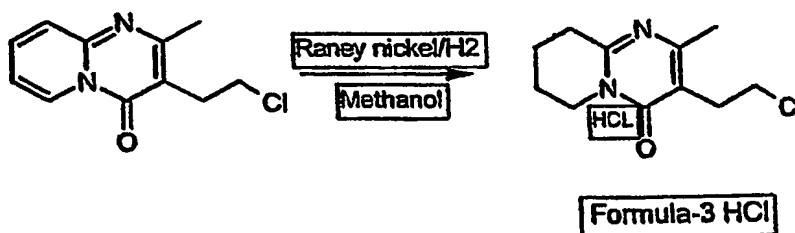


confirmed by the X-ray diffraction (XRD) analysis as shown in Figure - 1. This polymorphic form is designated as Form B in US-A-2002/0115672 (Mayers) and as Form A in WO-A-02/12200 (Teva). As shown by Figure 1, this polymorphic form has peaks at about 6.956, 10.630, 11.410, 14.188, 14.794, 15.428, 16.377, 18.453, 18.875, 19.750, 21.309, 22.121, 22.427, 23.152, 23.477, 24.303, 25.77, 27.507, 28.328, 28.965, 32.262, 33.005, 33.622, 38.488, 39.585, 42.705, 43.404 and  $45.059 \pm 0.2$  degrees two theta.

Risperidone base, thus crystallized, may be converted to pharmaceutically acceptable non-toxic acid addition salts such as hydrochloride, tartrate or palmate salts, by conventional methods.

The benzisoxazole compound of Formula -2 is preferably prepared according to the procedure described in the US-A-4,355,037.

The tetrahydropyrimidine compound of Formula -3 is preferably prepared by hydrogenation of the corresponding pyrimidine derivative 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2,a]pyrimidin-4-one, preferably in methanol using a Raney nickel catalyst according to Scheme -2.



**Scheme 2:**

The preferred hydrogenation reaction temperature is 28-35°C, and preferred hydrogen pressure 70-80 psi. The pyrimidine derivative itself prepared according to known procedures by the condensation of 2-aminopyridine with 2-acetylbutyrolactone.

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The present invention is further illustrated by the following non-limiting experimental examples:

#### EXAMPLES:

##### 10 Experimental details for preparation of risperidone

##### **Example 1: Condensation reaction in water medium**

6-Fluoro-3-(4-piperidiny)-1,2-benzisoxazole hydrochloride (Formula – 2.HCl, 100g) is added to a solution of sodium carbonate(180g) in 400ml water at 25-  
15 30°C. Slowly the reaction mass is warmed to 50-55°C and then a solution of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Formula – 3.HCl, 150g) in water (300ml) is added gradually over a period of 5 hours at 50-55°C. The reaction mass temperature is maintained further for another 4 hours. The reaction mass is cooled to room temperature and  
20 diluted with (200ml) water the precipitated risperidone is separated by filtration, washed with water (50ml ) and dried to get crude risperidone.

Crude risperidone weight = 135gm

Purity= 90-95% ( HPLC)

##### **Example 2: Condensation reaction in water medium**

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6-Fluoro-3-(4-piperidiny)-1,2-benzisoxazole hydrochloride (Formula – 2.HCl, 100g) is added to a solution of sodium carbonate(180g) in 400ml water at 25-  
30 30°C. Slowly the reaction mass is warmed to 50-55°C and then a solution of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Formula – 3.HCl, 150g) in water (300ml) is added gradually over a period of 5 hours at 50-55°C.. The reaction mass temperature is maintained further for another 4 hours. The reaction mass is cooled to room temperature and

diluted with (200ml) water the precipitated risperidone is extracted with dichloromethane (3x450ml). The dichloromethane extract is used for further work-up according to Method A or Method B, as given below to get crude risperidone.

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**Example 3: Condensation reaction in mixture of water and water-miscible solvents**

6-Fluoro-3-(4-piperidiny)-1,2 benzisoxazole hydrochloride (100g) is added to a  
10 suspension of sodium carbonate (180g) in acetonitrile (500ml) at 25-30°C. Slowly, the reaction mass is warmed to 70-75°C and then a solution of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (110g) in water (200ml) is added gradually over a period of 4 hours at 70-75°C. The reaction mass is maintained at the same temperature for an  
15 additional 4 hours. The reaction mass is then cooled to room temperature and diluted with water (500ml). The resulting mixture is extracted with dichloromethane (3x450ml). The dichloromethane extract is worked up as explained for Method A in Example 1 to produce crude risperidone

20 **Method A:** The dichloromethane extract is washed with 2x150ml of water, treated with activated carbon, and concentrated under reduced pressure to produce crude risperidone.

Crude risperidone: 190-200g

Purity: ~85-90% (HPLC)

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**Method B:** The dichloromethane extract is extracted with aqueous dilute hydrochloric acid (10%). The aqueous extract is washed with dichloromethane (200ml) and basified with aqueous ammonia to pH 8.5-9.0. The aqueous mass is extracted with dichloromethane (3x450ml), and the dichloromethane extract is  
30 washed with water, treated with activated carbon and then concentrated under reduced pressure to produce crude risperidone.

Crude risperidone: 180-190g  
Purity: ~87-92%(HPLC)

**Example 4: Purification of crude risperidone**

5 **A) From 10% aqueous acetone:**

Risperidone crude (100 g) is dissolved in 10% aqueous acetone (700ml) at 50-55°C, then treated with 10% activated carbon and filtered. The clear filtrate is gradually cooled to 0-5°C over a period of 4-5 hours. The crystallized risperidone is separated by filtration and washed with chilled 10% aqueous acetone followed by drying at 50-55°C under vacuum to get pure risperidone.

Pure risperidone: 75-80g  
Purity: >99%( HPLC)

**B) From 10% aqueous acetonitrile:**

15 Risperidone crude (100 g) is dissolved in 10% aqueous acetonitrile (500ml) at 65-70°C, then treated with 10% activated carbon and filtered. The clear filtrate is gradually cooled to 0-5°C over a period of 4-5 hours. The crystallized risperidone is separated by filtration and washed with chilled 10% aqueous acetonitrile followed by drying at 50-55°C under vacuum to get pure risperidone.

20 Pure risperidone: 80-85g  
Purity: >99% (HPLC)

**C) From 10% aqueous methyl ethyl ketone:**

25 Risperidone crude (100 g) is dissolved in 10% aqueous methyl ethyl ketone (600ml) at 65-70°C, then treated with 10% activated carbon and filtered. The clear filtrate is gradually cooled to 0-5°C over a period of 4-5 hours. The crystallized risperidone is separated by filtration and washed with chilled 10% aqueous methyl ethyl ketone followed by drying at 50-55°C under vacuum to get pure risperidone.

30 Pure risperidone: 65-70g  
Purity: >99% ( HPLC)

D) From 5% aqueous isobutyl methyl ketone:

Risperidone crude (100 g) is dissolved in 5% aqueous isobutyl methyl ketone (650ml) at 65-70°C, then treated with 10% activated carbon and filtered. The clear filtrate is gradually cooled to 0-5°C over a period of 4-5 hours. The

5 crystallized risperidone is separated by filtration and washed with chilled 10% aqueous isobutyl methyl ketone followed by drying at 50-55°C under vacuum to get pure risperidone.

Pure risperidone: 60-65g

Purity: >99%( HPLC)

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Crude risperidone is prepared using the same procedure as described in Example-3, but using different solvent media and temperature as given in Table-1, instead of acetonitrile (500ml) /water (200ml) at 70-75°C in Example-3, in the condensation reaction to get crude risperidone.

The above isolated crude risperidone is purified as disclosed in Example —4 :A,B,C and D.

The weights, yields & purities of pure risperidone (samples 1-8) are given in Table 1:

Sl. No	Solvent used for condensation reaction	Condensation reaction temperature (°C)	Weight (g)	Purity (%)	Yield (%)
1	Water	50-55	121	99.34	75.8%
2	Water:DMF (1.0:4.6 v/v)	55-60	110	99.67	68.76%
3	Water:DMF (1.0:7.0 v/v)	65-70	120	99.87	75%
4	Water:IPA (1.0:14.0 v/v)	60-65	80	99.67	50%
5	Water:MeOH (1.0:30.0 v/v)	60-65	80	99.74	50%
6	Water:ACN (1.0:4.0 v/v)	65-70	135	99.63	81.2%
7	Ethanol	65-70	115	99.72	67.5%
8	DMF	65-70	60	98.77	37.5%

**Example 5: Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one hydrochloride (Formula - 3**

**(1):Preparation of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one:**

2-Aminopyridine (100g) is added to a solution of toluene (100ml) and phosphorus  
5 oxychloride (365g) at 0-5°C and then the temperature is raised to 50-55°C.  
2-Acetylbutyrolactone (82g) is added to the mixture at the same temperature.  
The temperature is raised to 90-95°C and maintained for an additional 5 hours.  
Additional 2-acetylbutyrolactone (82g) is added at this temperature and the  
temperature is further maintained for an additional 9-10 hours. Toluene and the  
10 excess phosphorus oxychloride is then distilled off under reduced pressure and  
the residue is quenched over ice-water mixture. The pH of the resulting aqueous  
mixture is adjusted to 8-9 with liquor ammonia and the precipitated solid is  
extracted with dichloromethane (3x200ml). The organic extract is washed with  
water and then concentrated under reduced pressure to obtain a residue. The  
15 residue is triturated with isopropyl alcohol to produce 3-(2-chloroethyl)-2-  
methyl-4H-pyrido[1,2-a] pyrimidin-4-one.

**(2):Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one hydrochloride (Formula - 3)**

20 3-(2-Chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one(100gm) is taken in  
methanol(500ml) in a pressure reactor and Raney nickel(10g) added to it. The  
reactor is pressurised with hydrogen at 70 - 80psi and the mixture is stirred at 28-  
35°C until the hydrogen absorption ceases (approximately after 6 hours). The  
Raney nickel catalyst is then filtered. The pH of the filtrate is adjusted to 1.5-2.0  
25 with concentrated hydrochloric acid (50-60ml). Methanol is then distilled off under  
reduced pressure and isopropyl alcohol (500ml) is added to the residue. The  
resulting slurry is cooled to 0-5°C and the precipitated solid is filtered. The solid is  
washed with cold isopropyl alcohol and dried to produce 3-(2-chloroethyl)-  
6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride of  
30 Formula - 3.

Yield: 90g

Purity: >98% (by HPLC)